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<p>(54) Title: DERIVATIVES OF SUCCINAMIDE AND THEIR USE AS METALLOPROTEINASE INHIBITOR</p>		
<p>(57) Abstract</p> <p>Compounds of formula (I), wherein X is a -CO₂H or -CONHOH group; R₄ is a group -CHR^aR^y wherein R^a and R^y independently represent optionally substituted phenyl or monocyclic heteroaryl rings, which optionally may be linked covalently to each other by a bond or by a C₁-C₄ alkylene or C₂-C₄ alkenylene bridge; and R₁, R₂, R₃ and R₅ are as defined in the specification are selective inhibitors of stromelysin-1 and matrilysin relative to human fibroblast collagenase and 72KDa gelatinase.</p> <div data-bbox="990 1176 1380 1323"><p>Chemical structure (I) is a succinamide derivative. It consists of a four-membered ring with two carbonyl groups (C=O). The nitrogen atom of the ring is substituted with a hydrogen atom (H) and a group R₅. One of the carbonyl carbons is substituted with a group R₃. The other carbonyl carbon is substituted with a group R₂ and a group X. The group X is further substituted with a group R₁. The group R₄ is attached to the nitrogen atom of the succinamide ring.</p></div>		

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Derivatives of succinamide and their use as metalloproteinase inhibitor

The present invention relates to therapeutically active hydroxamic acid and carboxylic acid derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to the use of such compounds in medicine. In particular, the compounds are inhibitors of metalloproteinases involved in tissue degradation. Some of the compounds of the invention are, in addition, inhibitors of the release of tumour necrosis factor from cells.

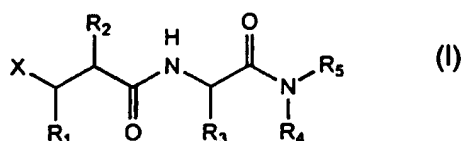
Background to the Invention

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown such as collagenases, stromelysins and/or gelatinases (known as "matrix metalloproteinases", and herein referred to as MMPs) are thought to be potentially useful for the treatment or prophylaxis of conditions involving such tissue breakdown, for example rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal or gastric ulceration, and tumour metastasis, invasion and growth. MMP inhibitors are also of potential value in the treatment of neuroinflammatory disorders, including those involving myelin degradation, for example multiple sclerosis, as well as in the management of angiogenesis dependent diseases, which include arthritic conditions and solid tumour growth as well as psoriasis, proliferative retinopathies, neovascular glaucoma, ocular tumours, angiofibromas and hemangiomas. However, the relative contributions of individual MMPs in any of the above disease states is not yet fully understood.

Metalloproteinases are characterised by the presence in the structure of a zinc(II) ionic site. It is now known that there exists a range of metalloproteinase enzymes that includes human fibroblast collagenase (Type 1), PMN-collagenase, 72 kDa-gelatinase, 92 kDa-gelatinase, stromelysin-1, stromelysin-2 and PUMP-1 (J.F. Woessner, FASEB J, 1991, 5, 2145-2154). Many known MMP inhibitors are peptide derivatives, based on naturally occurring amino acids, and are analogues of the

cleavage site in the collagen molecule. A paper by Chapman *et. al.* (J. Med. Chem. 1993, 36, 4293-4301) reports some general structure/activity findings in a series of N-carboxyalkyl peptides. Other known MMP inhibitors are less peptidic in structure, and may more properly be viewed as pseudopeptides or peptide mimetics. Such compounds usually have a functional group capable of binding to the zinc(II) site in the MMP, and known classes include those in which the zinc binding group is a hydroxamic acid, carboxylic acid, sulphhydryl, and oxygenated phosphorus (eg phosphinic acid and phosphoramidate including aminophosphonic acid) groups.

Two known classes of pseudopeptide or peptide mimetic MMP inhibitors have a hydroxamic acid group and a carboxylic group respectively as their zinc binding groups. With a few exceptions, such known MMPs may be represented by the structural formula (I)



in which X is the zinc binding hydroxamic acid (-CONHOH) or carboxylic acid (-COOH) group and the groups R₁ to R₅ are variable in accordance with the specific prior art disclosures of such compounds. Examples of patent publications disclosing such structures are given below.

In such compounds, it is generally understood in the art that variation of the zinc binding group and the substituents R₁, R₂ and R₃ can have an appreciable effect on the relative inhibition of the metalloproteinase enzymes. The group X is thought to interact with metalloproteinase enzymes by binding to a zinc(II) ion in the active site. Generally the hydroxamic acid group is preferred over the carboxylic acid group in terms of inhibitory activity against the various metalloproteinase enzymes. However, the carboxylic acid group in combination with other substituents can provide

selective inhibition of gelatinase (EP-489,577-A). The R_1 , R_2 and R_3 groups are believed to occupy respectively the P1, P1' and P2' amino acid side chain binding sites for the natural enzyme substrate. There is evidence that a larger R_1 substituent can enhance activity against stromelysin, and that a (C_1 - C_6)alkyl group (such as isobutyl) at R_2 may be preferred for activity against collagenase whilst a phenylalkyl group (such as phenylpropyl) at R_2 may provide selectivity for gelatinase over the other metalloproteinases.

The precise role of each of the various types of MMP in mediating different clinical disease conditions is not understood at present. However, there is some evidence that for some clinical end points individual MMP types may have a greater causative role than others. For the treatment of conditions mediated mainly by one MMP type, clearly it would be desirable to use an MMP inhibitor which selectively inhibited that MMP, or at least was significantly more potent as an inhibitor of that MMP than of other MMP types.

Tumour necrosis factor (herein referred to as "TNF") is a cytokine which is produced initially as a cell-associated 28kD precursor. It is released as an active, 17kD form, which can mediate a large number of deleterious effects in vivo. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase responses, similar to those seen during acute infections and shock states. Chronic administration can also cause cachexia and anorexia. Accumulation of excessive TNF can be lethal.

There is considerable evidence from animal model studies that blocking the effects of TNF with specific antibodies can be beneficial in acute infections, shock states, graft versus host reactions and autoimmune disease. TNF is also an autocrine growth factor for some myelomas and lymphomas and can act to inhibit normal haematopoiesis in patients with these tumours.

Compounds which inhibit the production or action of TNF are therefore thought to be

potentially useful for the treatment or prophylaxis of many inflammatory, infectious, immunological or malignant diseases. These include, but are not restricted to, septic shock, haemodynamic shock and sepsis syndrome, post ischaemic reperfusion injury, malaria, Crohn's disease, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, rheumatoid arthritis, multiple sclerosis, radiation damage, toxicity following administration of immunosuppressive monoclonal antibodies such as OKT3 or CAMPATH-1 and hyperoxic alveolar injury.

Since excessive TNF production has been noted in several diseases or conditions also characterised by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF production may have particular advantages in the treatment or prophylaxis of diseases or conditions in which both mechanisms are involved.

As mentioned above, MMP inhibitors have been proposed with hydroxamic acid or carboxylic acid zinc binding groups. The following patent publications disclose hydroxamic acid-based and/or carboxylic acid-based MMP inhibitors:

US 4599361	(Searle)
EP-A-0236872	(Roche)
EP-A-0274453	(Bellon)
WO 90/05716	(British Bio-technology)
WO 90/05719	(British Bio-technology)
WO 91/02716	(British Bio-technology)
EP-A-0489577	(Celltech)
EP-A-0489579	(Celltech)
EP-A-0497192	(Roche)
WO 92/13831	(British Bio-technology)
WO 92/17460	(SmithKline Beecham)
WO 92/22523	(Research Corporation Technologies)
WO 93/09090	(Yamanouchi)

WO 93/09097	(Sankyo)
WO 93/20047	(British Bio-technology)
WO 93/24449	(Celltech)
WO 93/24475	(Celltech)
EP-A-0574758	(Roche)
EP-A-0575844	(Roche)
WO 94/02446	(British Biotech)
WO 94/02447	(British Biotech)
WO 94/21612	(Otsuka)
WO 94/21625	(British Biotech)
WO 94/24140	(British Biotech)
WO 94/25434	(Celltech)
WO 94/25435	(Celltech)
WO 95/04033	(Celltech)
WO 95/04735	(Syntex)
WO 95/04715	(Kanebo)

Brief Description of the Invention

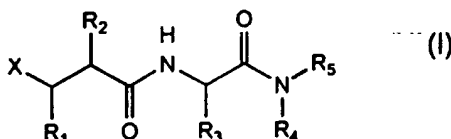
Pseudopeptide or peptide mimetic MMP inhibitors selectively active against stromelysins eg stromelysin-1, and against matrilysin, rather than collagenases eg human fibroblast collagenase, and gelatinases eg 72KDa gelatinase, do not appear to form part of the art. Such compounds would have value in allowing more precisely directed treatment of diseases and conditions mediated primarily by stromelysin-1 and matrilysin, rather than collagenases and gelatinases.

This invention makes available a class of compounds of formula (I) above wherein X is a hydroxamic acid or carboxylic acid group characterised primarily in that the R₄ substituent is a group -CHR^xR^y wherein R^x and R^y independently represent optionally substituted phenyl or monocyclic heteroaryl rings, which optionally may be linked covalently to each other by a bond or by a C₁-C₄ alkylene or C₂-C₄ alkenylene bridge. Such compounds are selective inhibitors of stromelysin-1 and matrilysin over

human fibroblast collagenase, and 72KDa gelatinase, ie are more active as inhibitors of stromelysin-1 than of human fibroblast collagenase, and 72KDa gelatinase.

Detailed Description of the Invention

The present invention provides compounds of general formula I



wherein

X is a -CO₂H or -CONHOH group;

R₁ is (C₁-C₆)alkyl; (C₂-C₆)alkenyl; phenyl; substituted phenyl; phenyl (C₁-C₆)alkyl; substituted phenyl(C₁-C₆)alkyl; heterocyclyl; substituted heterocyclyl; heterocyclyl(C₁-C₆)alkyl; substituted heterocyclyl(C₁-C₆)alkyl; a group BSO_nA- wherein n is 0, 1 or 2 and B is hydrogen or a (C₁-C₆) alkyl, phenyl, substituted phenyl, heterocyclyl, (C₁-C₆)acyl, phenacyl or substituted phenacyl group, and A represents (C₁-C₆)alkyl; amino; protected amino; acylamino; OH; SH; (C₁-C₆)alkoxy; (C₁-C₆)alkylamino; di-(C₁-C₆)alkylamino; (C₁-C₆)alkylthio; aryl (C₁-C₆)alkyl; amino(C₁-C₆)alkyl; hydroxy(C₁-C₆)alkyl, mercapto(C₁-C₆)alkyl or carboxy(C₁-C₆)alkyl wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated; lower alkyl substituted by carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, or carboxy-lower alkanoylamino;

R_2 is a (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl (C_1-C_6) alkyl, heteroaryl (C_1-C_6) alkyl, cycloalkyl (C_1-C_6) alkyl or cycloalkenyl (C_1-C_6) alkyl group, any one of which may be optionally substituted by one or more substituents selected from (C_1-C_6) alkyl, $-O(C_1-C_6)$ alkyl, $-OCH_2Ph$ wherein the phenyl group may be optionally substituted, $-S(C_1-C_6)$ alkyl, halo and cyano $(-CN)$;

R_3 is the characterising group of a natural or non-natural α amino acid in which any functional groups may be protected;

R_4 is a group $-CHR^*R^y$ wherein R^* and R^y independently represent optionally substituted phenyl or monocyclic heteroaryl rings, which optionally may be linked covalently to each other by a bond or by a C_1-C_4 alkylene or C_2-C_4 alkenylene bridge, either of which may be interrupted by an O or S atom;

R_5 is hydrogen or a (C_1-C_6) alkyl group;

or a salt, hydrate or solvate thereof.

As used herein the term " (C_1-C_6) alkyl" or "lower alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl and hexyl.

The term " C_1-C_4 alkylene bridge" means one of the following divalent moieties, namely $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

The term " (C_2-C_6) alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. This term would include, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

The term " C_2-C_4 alkenylene bridge" means one of the following divalent moieties,

namely $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CHCH}_2-$, $-\text{CH}_2\text{CH}=\text{CH}-$ or $-\text{CH}=\text{CHCH}_2\text{CH}_2-$, $\text{CH}_2\text{CH}=\text{CHCH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}-$, or $-\text{CH}=\text{CHCH}=\text{CH}-$.

The term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl and cyclopropyl.

The term "cycloalkenyl" means an unsaturated alicyclic moiety having from 4-8 carbon atoms and includes, for example, cyclohexenyl, cyclooctenyl, cycloheptenyl, cyclopentenyl, and cyclobutenyl. In the case of cycloalkenyl rings of from 5-8 carbon atoms, the ring may contain more than one double bond.

The unqualified term "heterocyclyl" or "heterocyclic" means (i) a 5-7 membered heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene ring, including for example, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, benzimidazolyl, maleimido, succinimido, phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidinyl or 2,6-dioxopiperidinyl, or (ii) a naphththalimido (ie 1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, or 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinolin-2-yl group.

The term "monocyclic heteroaryl" means a 5-7 membered substituted or unsubstituted aromatic heterocycle containing one or more heteroatoms. Illustrative of such rings are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C₁-C₆)alkyl, (C₁-C₆)alkoxy, hydroxy, mercapto, (C₁-C₆)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), nitro, trifluoromethyl, -COOH, -CONH₂, -CN, -COOR^A or -CONHR^AR^A wherein R^A is a (C₁-C₆)alkyl group or the residue of a natural alpha-amino acid.

The term "characterising group of a natural alpha-amino acid" means the characteristic side chain attached to the -CH(NH₂)(COOH) moiety in the following amino acids: glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid and aspartic acid.

Natural alpha-amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups in their characteristic side chains include arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine. When R₃ in the compounds of the invention is one of those side chains, the functional substituent may optionally be protected.

The term "protected" when used in relation to a functional substituent in a side chain of a natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. In this context, protected amino groups include amido and acylamino, protected hydroxy or mercapto groups include ethers and thioethers, protected carboxyl groups include esters, and imidazolyl, indolyl or guanidyl groups may be protected as t-butoxycarbonyl derivatives. These are only examples of the many protecting derivatives known in the art, and others will be known to the skilled man.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane

sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are several chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with R or S stereochemistry at each chiral centre. General formula (I), and (unless specified otherwise) all other formulae in this specification are to be understood to include all such stereoisomers and mixtures (for example racemic mixtures) thereof.

In the compounds of the invention, the preferred stereochemistry is in general as follows:

- C atom carrying the R_1 and X groups - S,
- C atom carrying the R_2 group - R,
- C atom carrying the R_3 group - S,
- C atom carrying the R^x and R^y groups - R or S

but mixtures in which the above configurations predominate are also contemplated.

As previously stated, the compounds of the invention are principally distinguished from the compounds disclosed in the prior art patent publications listed above by the identity of the group R_4 . Accordingly, the groups R_1 , R_2 , R_3 , and R_5 may be any of the groups which have been disclosed in the corresponding positions of compounds disclosed in any of those prior art patent publications listed above. Without limiting the generality of the foregoing, the following classes of substituent R_3 have been disclosed in the corresponding position of prior art compounds, and are therefore suitable R_3 groups for use in compounds of the present invention:

(C_1 - C_6)alkyl, benzyl, hydroxybenzyl, benzyloxybenzyl, (C_1 - C_6)alkoxybenzyl, or benzyloxy(C_1 - C_6)alkyl group; and

the characterising group of a natural α amino acid, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; and

a group $-[\text{Alk}]_n\text{R}_6$ where Alk is a $(\text{C}_1\text{-C}_6)$ alkyl or $(\text{C}_2\text{-C}_6)$ alkenyl group optionally interrupted by one or more -O-, or -S- atoms or -N(R₇)- groups [where R₇ is a

or (C₃-C₈)cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, phenyl(C₁-C₆)alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 3- to 8-membered heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, -CO₂H, (C₁-C₄)perfluoroalkyl, -CH₂OH, -CO₂(C₁-C₆)alkyl, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -S(C₁-C₆)alkyl, -SO(C₁-C₆)alkyl, -SO₂(C₁-C₆)alkyl, -S(C₂-C₆)alkenyl, -SO(C₂-C₆)alkenyl, -SO₂(C₂-C₆)alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO₂- and W represents a phenyl, phenylalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkylalkyl, (C₄-C₈)cycloalkenyl, (C₄-C₈)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO₂H, -CO₂(C₁-C₆)alkyl, -CONH₂, -CONH(C₁-C₆)alkyl, -CONH(C₁-C₆)alkyl)₂, -CHO, -CH₂OH, (C₁-C₄)perfluoroalkyl, -O(C₁-C₆)alkyl, -S(C₁-C₆)alkyl, -SO(C₁-C₆)alkyl, -SO₂(C₁-C₆)alkyl, -NO₂, -NH₂, -NH(C₁-C₆)alkyl, -N((C₁-C₆)alkyl)₂, -NHCO(C₁-C₆)alkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl, phenyl or benzyl.

More specifically with respect to the groups R₁, R₂, R₃, R₄ and R₅ in compounds of the invention:

Examples of particular R₁ groups include methyl, ethyl, hydroxyl, methoxy allyl, thienylsulphanylmethyl, thienylsulphinylmethyl, thienylsulphonylmethyl and phthalimidomethyl. Presently preferred are compounds in which R₁ is

hydroxyl, methoxy, allyl or phthalimidomethyl.

Examples of particular R_2 groups include iso-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, cyclohexylpropyl, phenylpropyl, phenylpropenyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, pyridine-4-ylpropyl, phenylbutyl, benzyloxybutyl, propyloxymethyl and propylsulphanyl. Presently preferred are compounds in which R_2 is isobutyl, n-octyl, n-decyl, phenylpropyl, or phenylpropenyl. Variation of the R_2 group may enhance the stromelysin-1 selectivity of a given compound relative not only to human fibroblast collagenase and 72KDa gelatinase, but also relative to matrilysin. For example, groups R_2 with chain lengths in excess of the equivalent of about 7 carbon atoms, eg n-octyl or longer, may be preferred over shorter R_2 groups, eg isobutyl, for such stromelysin-1 selectivity.

Examples of particular R_3 groups include benzyl, iso-butyl or t-butyl, 1-benzylthio-1-methylethyl, 1-hydroxy-1-methylethyl and 1-mercapto-1-methylethyl. Presently preferred are compounds in which R_3 is t-butyl, 1-hydroxy-1-methylethyl or 1-mercapto-1-methylethyl.

R_4 is a group $-\text{CHR}^x\text{R}^y$, and examples of R^x and R^y groups include optionally substituted phenyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, trizolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. Examples of particular R^x and R^y groups include phenyl, 2-fluorophenyl, 4-fluorophenyl, 2-pyridyl and 4-chlorophenyl. Also the R^x and R^y groups may be linked covalently to each other by a bond or by a $\text{C}_1\text{-C}_4$ alkylene or $\text{C}_2\text{-C}_4$ alkenylene bridge, and examples of such linked R^x and R^y groups include the case where R_4 is an optionally substituted 9-H-fluoren-9-yl group.

Examples of particular R_5 groups include hydrogen, methyl and ethyl. Presently preferred are compounds in which R_5 is hydrogen.

Specific examples of compounds of the present invention are:

N⁴-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-[1S-(9H-Fluoren-9-ylcarbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-(1S-[(4-Chloro-phenyl)-phenyl-methyl]-carbamoyl)-2,2-dimethyl-propyl)-2R,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-(1S-[(4-Fluoro-phenyl)-phenyl-methyl]-carbamoyl)-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3-isobutyl-succinamide;

N⁴-(1S-[(2-Fluoro-phenyl)-phenyl-methyl]-carbamoyl)-2,2-dimethyl-propyl)-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

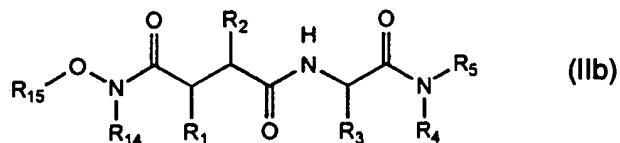
N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propylcarbamoyl]-2S-methoxy-5R-methyl-hexanoic acid;

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-2S,N¹-dihydroxy-2-isobutyl-3R-methoxy-succinamide;

N⁴-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-(3-phenyl-allyl)-succinamide;

N⁴-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-(3-phenyl-propyl)-succinamide;

(b) deprotecting a diprotected hydroxamic acid derivative of formula (IIb)



in which R_1 , R_2 , R_3 , R_4 , and R_5 are as defined in general formula (I), R_{14} is an amino protecting group and R_{15} is a hydroxyl protecting group.

For method (a) conversion of (II) to an activated derivative such as the pentafluorophenyl, hydroxysuccinyl, or hydroxybenzotriazolyl ester may be effected by reaction with the appropriate alcohol in the presence of a dehydrating agent such as dicyclohexyl dicarbodiimide (DCC), N,N-dimethylaminopropyl-N'-ethyl carbodiimide (EDC), or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ).

Protecting groups as referred to above are well known per se, for example from the techniques of peptide chemistry. Amino groups are often protectable by benzyloxycarbonyl, t-butoxycarbonyl or acetyl groups, or in the form of a phthalimido group. Hydroxy groups are often protectable as readily cleavable ethers such as the t-butyl or benzyl ether, or as readily cleavable esters such as the acetate. Carboxy groups are often protectable as readily cleavable esters, such as the t-butyl or benzyl ester.

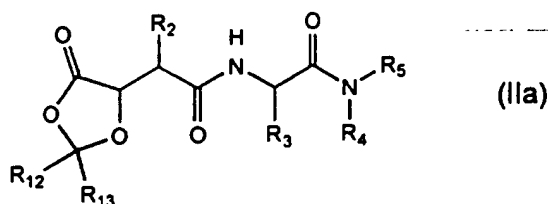
Examples of O-protected hydroxylamines for use in method (a) above include O-benzylhydroxylamine, O-4-methoxybenzylhydroxylamine, O-trimethylsilylhydroxylamine, and O-tert-butoxycarbonylhydroxylamine.

Examples of N,O-diprotected hydroxylamines for use in method (a) above include N,O-bis(benzyl)hydroxylamine, N,O-bis(4-methoxybenzyl)hydroxylamine, N-tert-butoxycarbonyl-O-tert-butyl dimethylsilylhydroxylamine, N-tert-butoxycarbonyl-O-

tetrahydropyranyloxyamine, and N,O-bis(tert-butoxycarbonyl)hydroxylamine.

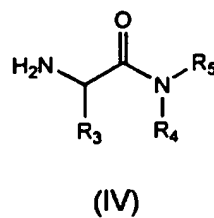
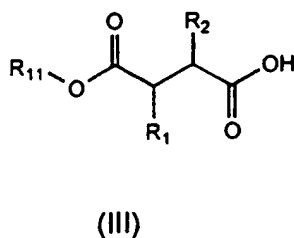
For method (b) suitable protecting groups R_{14} and R_{15} are benzyl and substituted benzyl (eg 4-methoxybenzyl). Such protecting groups may be removed by hydrogenolysis, while the 4-methoxybenzyl group may also be removed by acid hydrolysis.

In method (a) in the special case where R_1 in compound (I) is hydroxy, a particularly useful technique may be reaction of hydroxylamine with a dioxalone of formula (IIa):



wherein the groups R_{12} and R_{13} are derived from a dioxalone forming reagent, and may be, for example, hydrogen, alkyl, phenyl or substituted phenyl. The dioxalone ring is opened on reaction with hydroxylamine to give the required hydroxamic acid derivative of formula (I).

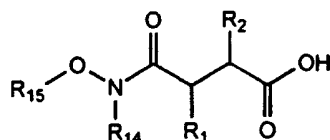
Compounds according to the present invention in which X is a carboxylic acid group -COOH may be prepared by a process comprising: coupling an acid of formula (III) or an activated derivative thereof with an amine of formula (IV)



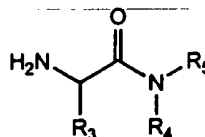
wherein R_1 , R_2 , R_3 , R_4 , and R_5 are as defined in general formula (I) except that any

substituents in R_1 , R_2 , R_3 , R_4 , and R_5 which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and R_{11} represents a hydroxy protecting group, and subsequently removing the protecting group R_{11} and any protecting groups from R_1 , R_2 , R_3 , R_4 , and R_5 .

Compounds of formula (IIb) may be prepared by a process comprising: causing an acid of formula (IIIa) or an activated derivative thereof to react with an amine of formula (IV)



(IIIa)



(IV)

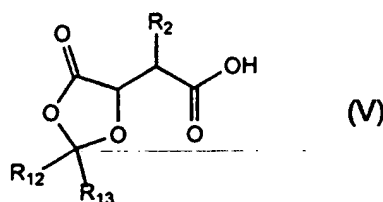
wherein R_1 , R_2 , R_3 , R_4 , and R_5 are as defined in general formula (I) except that any substituents in R_1 , R_2 , R_3 , R_4 , and R_5 which are potentially reactive in the coupling reaction may themselves be protected from such reaction, R_{14} is an amino protecting group and R_{15} is a hydroxyl protecting group as referred to in connection with formula (IIb) above, and subsequently removing any protecting groups from R_1 , R_2 , R_3 , R_4 , and R_5 .

Active derivatives of acids (III) and (IIIa) include activated esters such as the pentafluorophenyl ester, acid anhydrides and acid halides, eg chlorides. Suitable hydroxy protecting groups R_{11} may be selected from those known in the art.

Amine intermediates of formula (IV) are either known compounds or may be prepared from known amino acid starting materials and amines of formula HNR_4R_5 using standard methods. Where these amines HNR_4R_5 are not commercially available, they may be prepared in two steps from the corresponding ketones (W.R.

Roark *et al*, Bioorg. Med. Chem. 3, 29-39 (1995)).

In the special case where R_1 in compound (III) or (IIIa) is hydroxy, it too may be protected during the coupling of compounds (III) or (IIIa) and (IV). In the case where R_1 is hydroxy in compound (III) a particularly useful technique may be simultaneous protection of the two hydroxy groups as a dioxalone of formula (V):



wherein the groups R_{12} and R_{13} are derived from a dioxalone forming reagent, and may be, for example, hydrogen, alkyl, phenyl or substituted phenyl.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of MMPs, in particular stromelysin and matrilysin.

Accordingly in another aspect, this invention concerns a pharmaceutical or veterinary composition comprising a compound of formula (I) together with a pharmaceutically or veterinarily acceptable excipient or carrier. Included within this aspect of the invention is a pharmaceutical or veterinary composition comprising a compound of formula (I) together with a pharmaceutically or veterinarily acceptable excipient or carrier, characterised in that the composition is adapted for oral administration.

One or more compounds of general formula (I) may be present in the composition together with one or more excipient or carrier.

The compounds with which the invention is concerned may be prepared for

administration by any route consistent with their pharmacokinetic properties. Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

The dosage unit involved in oral administration may contain from about 1 to 250mg, eg from about 5 to 50mg of a compound of the invention.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceuticals such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or

suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The dosage for topical administration will of course depend on the size of the area being treated. For the eyes, each dose may typically be in the range from 10 to 100mg of the drug.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

For use in the treatment of rheumatoid arthritis, the drug can be administered by the oral route or by injection intra-articularly into the affected joint.

The following Examples illustrate embodiments of the invention:

The amino acids used in the examples were commercially available or were prepared according to literature procedures.

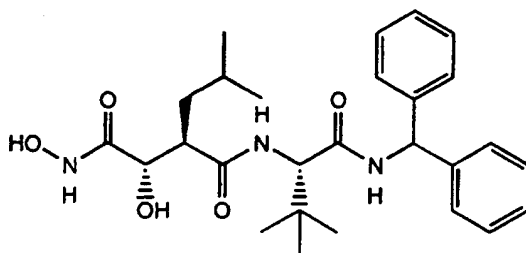
The following abbreviations have been used throughout:

DMF	N,N-Dimethylformamide
HOBt	1-Hydroxybenzotriazole
NMM	N-Methylmorpholine
TFA	Trifluoroacetic acid
EDC	N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride

^1H and ^{13}C NMR spectra were recorded using a Bruker AC 250E spectrometer at 250.1 and 62.9 MHz, respectively. Elemental microanalyses were performed by Medac Ltd. (Department of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PH).

EXAMPLE 1

N^4 -[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S, N^1 -dihydroxy-3R-isobutyl - succinamide



STEP A:

2R-(2,2-Dimethyl-5-oxo-[1,3]dioxolan-4S-yl)-4-methyl-pentanoic acid [1S-(benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-amide

To an ice-cooled solution of *L-tert-leucine-N-benzhydrylamide* (5.10 g, 17.29 mmol) in DMF (30 ml), was added 2R-(2,2-dimethyl-5-oxo-1-[1,3]dioxolan-4S-yl)-4-methyl-pentanoic acid 2,3,4,5,6-pentafluorophenyl ester (prepared according to WO 94/02447) (6.85 g, 17.29 mmol) in one portion. The reaction mixture was allowed to warm up to room temperature and was stirred overnight. The solvent was removed under pressure and the residue was dissolved in ethyl acetate (200 ml) and washed with 1M Na_2CO_3 (200 ml) and brine (200 ml). The organic phase was separated, dried over anhydrous MgSO_4 , filtered and concentrated to a white foam. The product was obtained as a white solid (3.82 g, 50%) following recrystallisation from ethyl acetate-hexane. ^1H -

NMR; δ (CDCl_3), 7.37 - 7.18 (10H, m), 6.53 (1H, d, $J = 9.3$ Hz), 6.47 (1H, d, $J = 7.7$ Hz), 6.21 (1H, d, $J = 7.9$ Hz), 4.39 (1H, d, $J = 5.9$ Hz), 4.27 (1H, d, $J = 9.0$ Hz), 2.72 - 2.66 (1H, m), 1.77 - 1.50 (9H, m), 1.01 (9H, s), 0.90 (3H, d, $J = 6.3$ Hz) and 0.87 (3H, d, $J = 6.1$ Hz).

STEP B:

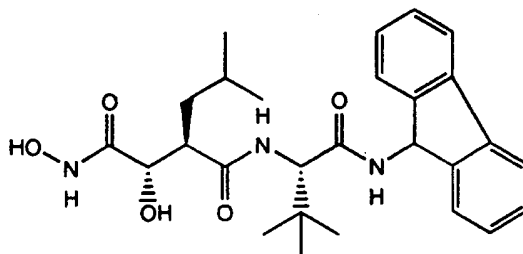
N^4 -[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S, N^1 -dihydroxy-3R-isobutyl - succinamide

To a solution of hydroxylamine hydrochloride (2.61 g, 37.61 mmol) in methanol (50 ml), sodium methoxide (2.03 g, 37.61 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature and then filtered to remove undissolved material. The filtrate was added to an ice-cooled solution of 2R-(2,2-dimethyl-5-oxo-[1,3]dioxolan-4S-yl)-4-methyl-pentanoic acid [1S-(benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-amide in a mixture of DMF (10 ml) and methanol (30 ml). The reaction mixture was allowed to warm up to room temperature and was stirred overnight. The solvent was removed under reduced pressure and the residue were partitioned between ether (50 ml) and water (50 ml). The mixture was allowed to stand at room temperature overnight. The product was collected by filtration and washed with water and ether to leave a white crystalline solid (2.77 g, 76%). m.p. 200.5 - 201°C. $^1\text{H-NMR}$; δ (CD_3OD), 8.88 (1H, d, $J = 8.3$ Hz), 7.84 (1H, d, $J = 9.3$ Hz), 7.22 (10H, m), 6.16 (1H, m), 4.40 (1H, m), 3.95 (2H, d, $J = 6.9$ Hz), 2.84 (1H, m), 1.63 (1H, m), 1.55 (1H, m), 1.13 (1H, m), 0.95 (9H, s) and 0.81 (6H, d, $J = 6.4$ Hz). $^{13}\text{C-NMR}$; δ (CD_3OD), 175.6, 171.8, 171.6, 142.8, 129.6, 129.4, 129.1, 128.5, 128.2, 73.3, 62.0, 58.0, 49.5, 39.3, 35.8, 27.2, 27.0, 24.0 and 22.2. IR; ν_{max} (KBr), 3366, 2943, 1643, 1519, 1378 and 700 cm^{-1} . Found: C 65.55, H 7.59, N 8.52% ; $\text{C}_{27}\text{H}_{37}\text{N}_3\text{O}_5 \cdot 0.6\text{H}_2\text{O}$ requires: C 65.59, H 7.79, N 8.50%.

The following additional compounds were prepared according to the methods of Example 1:

EXAMPLE 2

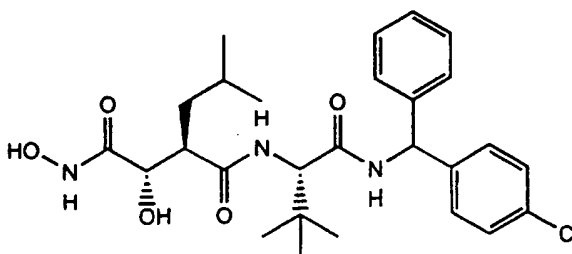
N⁴-[1S-(9H-Fluoren-9-ylcarbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-isobutyl-succinamide



White solid. m.p. 209 - 211° ¹H-NMR; δ (CD₃OD), 8.53 (1H, d, J = 8.5 Hz), 7.96 (1H, d, J = 9.3 Hz), 7.69 (2H, d, J = 7.4 Hz), 7.43 (2H, d, J = 7.3 Hz), 7.23 (4H, m), 6.04 (1H, d, J = 8.2 Hz), 4.33 (1H, m), 4.00 (1H, d, J = 6.8 Hz), 2.89 (1H, m), 1.59 (2H, m), 1.19 (1H, m), 1.05 (9H, s), 0.92 (3H, d, J = 6.4 Hz) and 0.88 (3H, d, J = 6.5 Hz). ¹³C-NMR; δ (CD₃OD), 175.5, 173.5, 171.6, 145.6, 145.3, 142.1, 141.9, 129.7, 128.7, 126.2, 126.0, 121.1, 121.0, 73.3, 62.3, 55.7, 49.5, 39.5, 35.5, 27.3, 27.1, 24.0 and 22.3. IR; ν_{\max} (KBr), 3305, 2858, 1651, 1520, 1369, 1069 and 737 cm⁻¹. Found C 66.14, H 7.20, N 8.45%; C₂₇H₃₅N₃O₅ · 0.5 H₂O requires C 66.10, H 7.40, N 8.56 %.

EXAMPLE 3

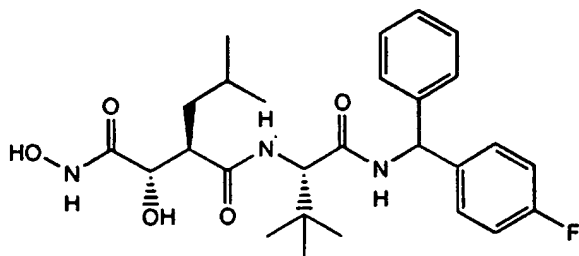
N⁴-(1S-[(4-Chloro-phenyl)-phenyl-methyl]-carbamoyl)-2,2-dimethyl-propyl)-2R,N¹-dihydroxy-3R-isobutyl-succinamide



White powder. m.p. 192 -194°C. $^1\text{H-NMR}$; δ (CD_3OD), 8.48 (1H, d, $J = 7.9$ Hz), 7.21 (9H, m), 6.17 (1H, m), 4.00 (1H, d, $J = 5.7$ Hz), 2.81 (1H, m), 1.59 (1H, m), 1.46 (1H, m), 1.24 (1H, m), 1.02 (1H, m), 0.95 (9H, s), 0.89 (3H, d, $J = 6.4$ Hz), and 0.81 (3H, d, $J = 6.4$ Hz). $^{13}\text{C-NMR}$; δ (CD_3OD), 175.6, 171.9, 171.6, 142.8, 129.6, 129.4, 129.1, 128.5 (2s), 128.2, 73.3, 61.9, 58.0, 49.5, 39.3, 35.7, 27.2, 27.0, 24.0 and 22.2. IR; ν_{max} (KBr), 3300, 2942, 1637, 1519, 1367 and 697 cm^{-1} .

EXAMPLE 4

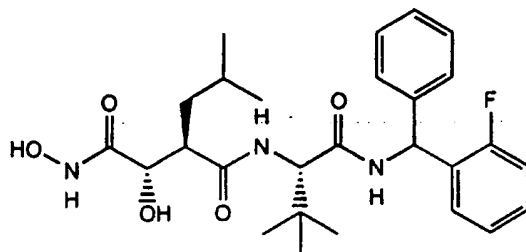
N^4 -(1S-[[[(4-Fluoro-phenyl)-phenyl-methyl]-carbamoyl]-2,2-dimethyl-propyl]-2S, N^1 - dihydroxy-3-isobutyl-succinamide



White solid (mixture of diastereomers). m.p. 118-125°C. $^1\text{H-NMR}$; δ (CDCl_3): 9.68 (1H, br s), 8.05 (1H, br m), 7.27 (4H, m), 7.15 (3H, m), 6.99 (2H, t, $J = 8.6$ Hz), 6.85 (1H, dd, $J = 7.6$ Hz), 6.22 (1H, d, $J = 7.4$ Hz), 5.30 (1H, br s), 4.31 (1H, d, $J = 9.3$ Hz), 4.12 (1H, s), 3.32 (1H, br m), 1.75 (1H, m), 1.41 (2H, m), 0.92 (9H, s) and 0.84 (6H, dd, $J = 2.8$ Hz). $^{13}\text{C-NMR}$; δ (CDCl_3): 174.9, 169.5, 168.5, 140.8, 140.6, 137.0, 129.3, 129.2, 128.9, 128.8, 128.7, 127.8, 127.6, 127.5, 127.1, 115.7, 115.5, 115.5, 115.3, 77.5, 73.1, 61.2, 56.5, 56.4, 44.7, 39.0, 34.9, 26.6, 25.9, 22.8 and 22.1. IR; ν_{max} (KBr) 3300, 2958, 2871, 1640, 1509, 1159, 1015 and 976 cm^{-1} .

EXAMPLE 5

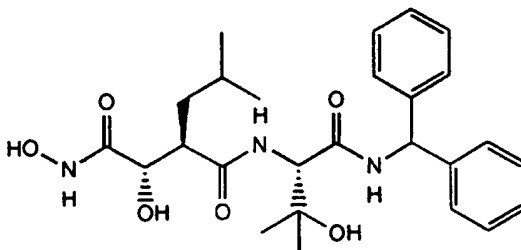
N⁴-(1S-[(2-Fluoro-phenyl)-phenyl-methyl]-carbamoyl)-2,2-dimethyl-propyl)-2S,N¹ - dihydroxy-3R-isobutyl-succinamide



White solid (mixture of diastereomers). m.p. 150-151°C. ¹H-NMR; δ (CD₃OD): 8.81 (0.5H, d, J = 8.3Hz), 8.75 (0.5H, d, J = 8.1Hz), 7.79 (0.5H, d, J = 9.2Hz), 7.74 (0.5H, d, J = 9.8Hz), 7.27-6.91 (9H, m), 6.39 (0.5H, d, J = 8.4Hz), 6.31 (0.5H, d, J = 8.1Hz), 4.34 (0.5H, s), 4.30 (0.5H, s), 3.89 (0.5H, d, J = 7.1Hz), 3.85 (0.5H, d, J = 7.4Hz), 2.73 (1H, m), 1.55-1.02 (3H, m), 0.90 (4.5H, s), 0.87 (4.5H, s), 0.76 (3H, d, J = 6.5Hz), and 0.70 (3H, dd, J = 3.9, 6.6Hz). ¹³C-NMR; δ (CD₃OD): 175.5, 171.8, 171.7, 171.6, 162.8, 162.7, 160.9, 160.8, 141.6, 141.6, 130.6, 130.6, 130.5, 130.3, 130.3, 129.6, 129.5, 129.5, 128.6, 128.6, 128.4, 128.2, 125.3, 125.3, 125.3, 116.5, 116.4, 116.3, 116.2, 73.3, 73.2, 61.92, 61.8, 52.5, 52.4, 51.7, 51.6, 49.4, 39.3, 39.0, 35.6, 27.2, 27.1, 27.0, 26.9, 26.9, 24.0, 23.9, 22.2 and 22.0. Found: C 63.16, H 7.20, N 7.95%; C₂₇H₃₆FN₃O₅·0.7H₂O requires: C 63.07, H 7.33, N 8.17%.

EXAMPLE 6

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-2S,N¹-dihydroxy-3R - isobutyl-succinamide



STEP A:**2R,3-Dihydroxy-3-methyl-butyric acid ethyl ester**

A suspension of Admixα (Trade Mark) (Aldrich, 90 g) in *tert*-butanol-water (1:1, 600 ml) was stirred vigorously at room temperature for 5 minutes. Methane sulphonamide (6 g, 63.08 mmol) was then added and the mixture cooled to 0°C. 3-Methyl-but-2-enoic acid ethyl ester (9.5 ml, 80.67 mmol) was added and stirring was continued at 0°C for 9 hours then at room temperature overnight. Solid Na₂SO₃ (90 g) was added and stirring was continued for 1 hour. The reaction mixture was diluted with ethyl acetate (200 ml) and transferred to a separating funnel. The organic layer was removed and the aqueous phase extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed successively with 1N NaOH (200 ml) and brine (200 ml), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate in hexane) to give the title compound as a colourless oil (7.77 g, 60%). ¹H-NMR; δ (CDCl₃): 4.29 (2H, ddd, J = 14.2, 7.2, 3.1 Hz), 3.95 (1H, d, J = 6.8 Hz), 3.33 (1H, d, J = 6.8 Hz), 2.76 (1H, s), 1.13 (3H, t, J = 7.2 Hz), 1.29 (3H, s) and 1.21 (3H, s). IR; ν_{max} (neat) 3439, 2980, 2938, 1731, 1372, 1270 and 1093. [α_D]²⁰ = -18.35 (c = 2, CH₂Cl₂).

STEP B:**5,5-Dimethyl-2,2-dioxo-[1,3,2]dioxathiolane-4R-carboxylic acid ethyl ester**

Thionyl chloride (3.4 ml, 46.66 mmol) was added dropwise to a solution of 2R-2,3-dihydroxy-3-methyl-butyric acid ethyl ester (6.3 g, 38.89 mmol) in carbon tetrachloride (50 ml) and the resulting solution was heated at reflux for 2 hours. The reaction mixture was cooled to 0°C and acetonitrile (50 ml), RuCl₃·H₂O (7 mg), NaIO₄ (12.5 g, 58.32

mmol) and water (60 ml) were added. The resulting orange mixture was stirred at room temperature for 3 hours, poured into ether (120 ml) and the phases separated. The aqueous layer was extracted with ether (2 x 60 ml). The combined organic layers were washed successively with water (2 x 30 ml), saturated aqueous NaHCO_3 (30 ml) and brine (30 ml), dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure to provide the title compound as a colourless oil (7.15 g, 82%). $^1\text{H-NMR}$; δ (CDCl_3): 5.03 (1H, s), 4.34 (2H, dd, $J = 14.3, 7.0$ Hz), 1.79 (3H, s), 1.57 (3H, s) and 1.35 (3H, t, $J = 7.0$ Hz).

STEP C:

2S-Azido-3-hydroxy-3-methyl-butyric acid ethyl ester

To a solution of 5,5-dimethyl-2,2-dioxo-[1,3,2]dioxathiolane-4R-carboxylic acid ethyl ester (2.0 g, 8.93 mmol) in (10:1) acetone:water (20 ml) was added NaN_3 (1.16 g, 18.75 mmol) and the mixture stirred vigorously at room temperature for 24 hours. Solvents were removed *in vacuo* and the residue treated with 20% aqueous H_2SO_4 (40 ml) and ether (40 ml) and vigorously stirred at room temperature for a further 24 hours. The ether layer was separated and the aqueous phase extracted with ether (3 x 10 ml). The combined organic layers were dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, 20% ethyl acetate in hexane) to provide the title compound as a colourless oil (1.0 g, 60%). $^1\text{H-NMR}$; δ (CDCl_3): 4.30 (2H, dd, $J = 14.3, 7.2$ Hz), 3.78 (1H, s), 2.97 (1H, s), 1.34 (3H, t, $J = 7.3$ Hz) and 1.29 (6H, s). IR; ν_{max} (neat) 3534 (br), 2989, 2944, 2111, 1766, 1466, 1378, 1297 and 1058. $[\alpha_D]^{20} = +20.55$ ($c = 2, \text{CH}_2\text{Cl}_2$).

STEP D:

2S-Azido-3-hydroxy-3-methyl-butyric acid

To a solution of 2-azido-3-hydroxy-3-methyl-butyric acid ethyl ester (4.75 g, 25.40

mmol) in tetrahydrofuran at 0°C was added a 1M aqueous solution of NaOH (26 ml, 26 mmol). The reaction mixture was stirred at 0°C for 3 hours then diluted with ether (50 ml). The organic layer was separated and the aqueous phase extracted with ether (50 ml) then cooled to 0°C, acidified to pH 2 by dropwise addition of conc. HCl and extracted with ethyl acetate (5 x 100 ml). The combined organic extracts were dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo* to provide the title compound as a pale yellow oil (2.65 g, 66%). $^1\text{H-NMR}$; δ (CDCl_3): 6.76 (2H, br s), 3.92 (1H, s), 1.37 (3H, s) and 1.34 (3H, s). IR; ν_{max} (CCl_4), 3565 (br), 2978, 2120, 1737, 1719, 1548, 1243 and 1002. $[\alpha_D]^{20} = +17.95$ ($c = 2$, CH_2Cl_2).

STEP E:

2S-Azido-N-benzhydryl-3-hydroxy-3-methyl-butyramide

A solution of 2S-azido-3-hydroxy-3-methyl-butyric acid (1.3 g, 8.18 mmol) in DMF (30 ml) was cooled to 0°C and treated with HOBt (1.32 g, 9.81 mmol) and EDC (1.88 g, 9.81 mmol). The reaction mixture was allowed to warm slowly to room temperature and stirred for three hours. C,C-Di-phenyl-methylamine (2.82 ml, 16.35 mmol) was added and the reaction mixture was stirred at room temperature overnight. Solvent was evaporated and the residue dissolved in dichloromethane (50 ml). The solution was washed successively with 1N aqueous HCl (2 x 30 ml), saturated aqueous NaHCO_3 (2 x 30 ml) and brine (30 ml), dried over anhydrous MgSO_4 , filtered and concentrated to a yellow oil. The crude product was purified by column chromatography (silica gel, 40% ethyl acetate in hexane) to give the title compound as a colourless oil (1.86 g, 70%). $^1\text{H-NMR}$; δ (CDCl_3): 7.31 (11H, m), 6.24 (1H, d, $J = 8.2$ Hz), 4.23 (1H, s), 3.89 (1H, s), 1.33 (3H, s) and 1.20 (3H, s).

STEP F:

2S-Amino-N-benzhydryl-3-hydroxy-3-methyl-butyramide

To a solution of 2S-azido-N-benzhydryl-3-hydroxy-3-methyl-butyramide (1.86 g, 5.74 mmol) in methanol (20 ml) was added 20% Pd(OH)₂ on carbon (300 mg). The reaction mixture was vigorously stirred under an atmosphere of H₂ gas at room temperature and atmospheric pressure for 36 hours. The mixture was filtered through celite, washing well with methanol and the filtrate concentrated *in vacuo* to provide the title compound as an off-white solid (1.63 g, 96%). ¹H-NMR; δ (CD₃OD): 7.21 (10H, m), 6.17 (1H, s), 3.71 (1H, s), 1.21 (3H, s) and 1.11 (3H, s).

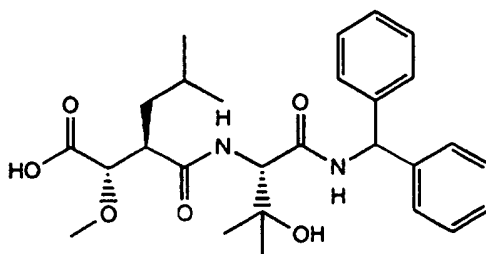
The title compound was then prepared from 2S-amino-N-benzhydryl-3-hydroxy-3-methyl-butyramide by methods analogous to those described in Example 1:

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-2S,N¹-dihydroxy-3R - isobutyl-succinamide

White solid. m.p. 201-202°C. ¹H-NMR; δ (CD₃OD), 7.19 (10H, m), 6.09 (1H, s), 4.41 (1H, s), 3.87 (1H, d, J = 7.2 Hz), 2.75 (1H, m), 1.52 (1H, m), 1.35 (1H, m), 1.13 (3H, s), 1.10 (3H, s), 1.06 (1H, m) and 0.73 (6H, dd, J = 6.4, 2.1 Hz). ¹³C-NMR; δ (CD₃OD): 178.8, 174.0, 145.2, 145.1, 131.9, 131.8, 131.2, 130.9, 130.8, 130.7, 75.7, 75.3, 63.8, 60.6, 41.5, 30.1, 29.3, 28.8, 26.3 and 24.5. IR; ν_{\max} (KBr) 3307, 2954, 1637, 1531, 1466, 1384, 1208, 1072 and 696 cm⁻¹.

EXAMPLE 7

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propylcarbamoyl]-2S-methoxy-5R-methyl-hexanoic acid



STEP A:**2S-Hydroxy-3R-isobutyl-succinic acid dimethyl ester**

2R-(2,2-Dimethyl-5-oxo-[1,3]-dioxalan-4S-yl)-4-methyl-pentanoic acid (75.0 g, 0.326 mol) was dissolved in methanol (500 ml) and cooled to 0°C and the resulting solution was saturated with hydrogen chloride gas. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane and washed successively with saturated NaHCO₃ and brine. The organic layer was dried (anhydrous MgSO₄), filtered and evaporated to dryness under reduced pressure to give the title compound (53 g, 75%). ¹H-NMR; δ (CDCl₃), 4.10 (1H, d, J = 4.0 Hz), 3.60 (3H, s), 3.50 (3H, s), 2.82 - 2.74 (1H, m), 1.61 - 1.40 (2H, m), 1.33 - 1.23 (1H, m) and 0.76 - 0.73 (6H, m).

STEP B:**2R-isobutyl-3S-methoxy-succinic acid dimethyl ester**

2S-Hydroxy-3R-isobutyl-succinic acid dimethyl ester (9.6 g 44 mmol) was dissolved in DMF (5 ml) and distilled iodomethane (3.3 ml) and silver (I) oxide (11.2 g) were added. The reaction was stirred with the exclusion of light for 5 days at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, dichloromethane) to give the title compound as a yellow viscous liquid, 4.7 g (46%). ¹H-NMR; δ (CDCl₃), 3.83 (1H, d, J = 7.5 Hz), 3.71 (3H, s), 3.62 (3H, s), 3.30 (3H, s), 2.89 - 2.80 (1H, m), 1.65 - 1.39 (2H, m), 1.15 - 1.04 (1H, m) and 0.83 - 0.81 (6H, m).

STEP C:**2R-Isobutyl-3S-methoxy-succinic acid dilithium salt**

Lithium hydroxide (1.76 g, 42.0 mmol) was added to a solution of 2R-isobutyl-3S-methoxy-succinic acid dimethyl ester (4.70 g, 20.0 mmol) in methanol (30 ml) and water (30 ml). The reaction mixture was stirred at room temperature for 2 hours then solvents were removed under reduced pressure to give the product as a yellow solid (4.40 g, 100%). ¹H-NMR; δ (CD₃OD), 3.52 (1H, d, J = 5.1 Hz), 3.27 (3H, s), 2.69 - 2.61 (1H, m), 1.56 - 1.53 (2H, m), 1.34 - 1.28 (1H, m) and 0.82 - 0.78 (6H, m).

STEP D:

2R-Isobutyl-3S-methoxy-succinic acid 4-methyl ester

2R-Isobutyl-3S-methoxy-succinic acid dilithium salt (4.40 g, 20.0 mmol) was dissolved in THF (30 ml), the solution was cooled to 0°C and trifluoroacetic anhydride (30 ml) was added. The reaction was stirred for 4 hours, the solvent was removed under reduced pressure and the residue was dissolved in methanol (2 ml) at 0°C and stirred to room temperature overnight. The solvent was removed under reduced pressure to give the title compound as a yellow oil (7.0 g, including residual salts), which was used without further purification in STEP E. ¹H-NMR; δ (CD₃OD), 7.61 (1H, d, J = 7.5 Hz), 3.65 (3H, s), 3.24 (3H, s), 2.78 - 2.67 (1H, m), 1.56 - 1.42 (2H, m), 1.09 - 1.03 (1H, m) and 0.81 - 0.79 (6H, m).

STEP E:

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propylcarbamoyl]-2S-methoxy-5R-methyl-hexanoic acid methyl ester

A solution of 2-isobutyl-1-methoxy-succinic acid 1-methyl ester (0.33 g, 1.67 mmol) in DMF (10 ml) was cooled to 0°C and treated with HOBt (0.27 g, 2.01 mmol) and EDC (0.38 g, 2.01 mmol). The reaction mixture was allowed to warm slowly to room temperature and stirred for three hours. 2-Amino-N-benzhydryl-3-hydroxy-3-methyl-butyramide (0.5 g, 1.67 mmol) was added and the reaction mixture was stirred at 40°C

overnight. Solvent was evaporated and the residue dissolved in dichloromethane (25 ml). The solution was washed successively with 1N aqueous HCl (2 x 15 ml), saturated aqueous NaHCO₃ (2 x 15 ml) and brine (15 ml), dried over anhydrous MgSO₄, filtered and concentrated to a yellow gum. Trituration with ether provided the title compound as a white solid (220 mg, 27%). ¹H-NMR; δ (CDCl₃): 7.52 (1H, d, J = 8.2 Hz), 7.26 (10H, m), 6.87 (1H, d, J = 8.6 Hz), 6.25 (1H, d, J = 7.9 Hz), 4.41 (1H, d, J = 8.9 Hz), 3.82 (1H, d, J = 6.1 Hz), 3.62 (3H, s), 3.30 (3H, s), 2.73 (1H, m), 1.62 (3H, m), 1.47 (1H, m), 1.29 (3H, s), 1.17 (3H, s) and 0.86 (6H, dd, J = 6.5, 4.6 Hz).

STEP F:

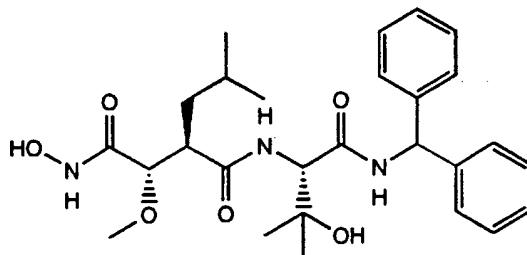
N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propylcarbamoyl]-2S-methoxy-5R-methyl-hexanoic acid

To a solution of N⁴-[1S-(benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propylcarbamoyl]-2S-methoxy-5R-methyl-hexanoic acid methyl ester (0.2 g, 0.418 mmol) in 3:2 tetrahydrofuran:water (5 ml) was added LiOH.H₂O (18.5 mg, 0.44 mmol) and the solution stirred at room temperature for 2 hours. The reaction mixture was then acidified to pH 1 with 1N aqueous HCl, and extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to provide the title compound as a white solid (180 mg, 93%). m.p. 118-119°C. ¹H-NMR; δ (CD₃OD): 8.60 (2H, d, J = 8.2Hz), 8.03 (1H, d, J = 9.15Hz), 7.19 (10H, m), 6.10 (1H, d, J = 8.3Hz), 4.42 (1H, d, J = 9.1Hz), 3.64 (1H, d, J = 8.9Hz), 2.71 (1H, m), 1.55 (1H, m), 1.29 (1H, m), 1.13 (3H, s), 1.11 (3H, s), 1.02 (1H, m), and 0.72 (6H, d, J = 6.5Hz). ¹³C-NMR; δ (CD₃OD): 175.1, 174.6, 171.59, 142.7, 129.5, 129.5, 128.9, 128.4, 128.3, 128.3, 83.8, 72.9, 61.3, 58.5, 58.2, 48.9, 38.2, 27.6, 27.2, 26.1, 23.9 and 21.9.

EXAMPLE 8

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-2S,N¹-dihydroxy-2-isobutyl-

3R-methoxy-succinamide

**STEP A:**

N 1-[1-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-N 4-benzyloxy-2-isobutyl-3-methoxy-succinamide

A solution of N 4-[1-(benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propylcarbamoyl]-2-methoxy-5-methyl-hexanoic acid (160 mg, 0.33 mmol) in anhydrous tetrahydrofuran (5 ml) was cooled to -10°C and treated with NMM (0.045 ml, 0.4 mmol) then isobutyl chloroformate (0.052 ml, 0.4 mmol), and the reaction mixture stirred at -10°C for 20 minutes. O-Benzyl hydroxylamine (50 mg, 0.4 mmol) was added and stirring was continued at -10°C for 2.5 hours. Solvent was removed *in vacuo* and trituration with ethyl acetate and hexane provided the title compound as a white solid (130 mg, 67%).
¹H-NMR; δ (CDCl₃): 8.20 (1H, d, J = 8.1 Hz), 7.52 (1H, d, J = 9.1 Hz), 7.31 (15H, m), 6.13 (1H, d, 8.1 Hz), 4.84 (2H, s), 4.49 (1H, d, J = 9.1 Hz), 3.66 (1H, d, J = 7.5 Hz), 3.11 (3H, s), 2.82 (2H, br m), 1.58 (1H, m), 1.36 (1H, m), 1.24 (1H, m), 1.20 (3H, s), 1.11 (3H, s) and 0.78 (6H, d, J = 6.5 Hz).

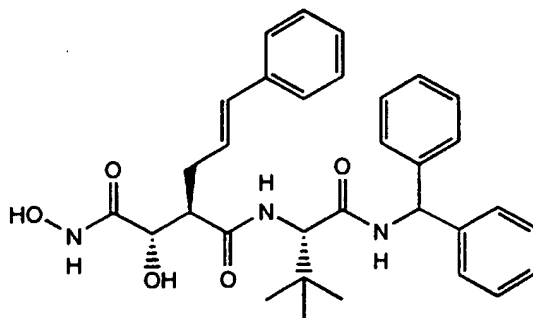
STEP B:

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-2,N¹-dihydroxy-2R-isobutyl-3S-methoxy-succinamide

To a solution of N'-[1S-(benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-N⁴-benzyloxy-2R-isobutyl-3S-methoxy-succinamide (130 mg, 0.22 mmol) in methanol (10 ml) was added 10% Pd on carbon (20 mg). The reaction mixture was vigorously stirred under an atmosphere of H₂ gas at room temperature and atmospheric pressure for 3 hours. The mixture was then filtered through celite, washing well with methanol and the filtrate concentrated *in vacuo* to provide the title compound as a pale yellow solid (80 mg, 73%). m.p. 148.6-149°C. ¹H-NMR; δ (CD₃OD): 7.17 (10H, m), 6.08 (1H, s), 4.44 (1H, s), 3.45 (1H, d, J=9.5Hz), 3.13 (3H, s), 2.70 (1H, m), 1.45 (1H, m), 1.32 (1H, m), 1.14 (3H, s), 1.10 (3H, s), 0.90 (1H, m) and 0.70 (6H, d, J=6.5Hz). ¹³C-NMR; δ (CD₃OD): 175.2, 171.5, 169.3, 142.8, 129.5, 129.5, 128.9, 128.7, 128.5, 128.4, 128.3, 83.1, 72.9, 61.4, 58.2, 58.0, 48.9, 38.3, 27.8, 26.9, 26.1, 24.2 and 21.8.

EXAMPLE 9

N⁴-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-(3-phenyl-allyl)-succinamide

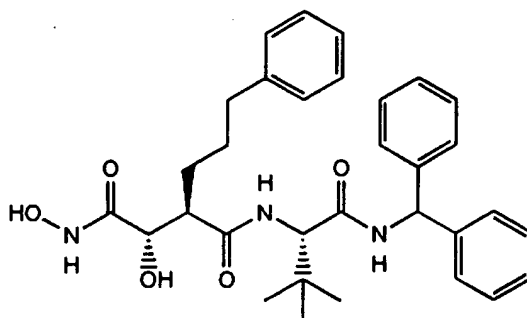


White solid (mixture of diastereomers). m.p. 97-99°C. ¹H-NMR; δ (CD₃OD), 7.21-6.99 (15H, m), 6.36-6.30 (1H, m), 6.15-5.98 (2H, m), 4.38 (0.6H, s), 4.29 (0.4H, s), 4.26 (0.4H, d, J = 4.4Hz), 4.12 (0.6H, d, J = 6.1Hz), 2.99-2.92 (1H, m), 2.54-2.32 (2H, m), 0.87 (6H, s) and 0.78 (3H, s). ¹³C-NMR; δ (CD₃OD), 175.0, 171.9, 171.5, 143.1, 138.8, 133.7, 129.5, 129.2, 128.6, 128.5, 127.4, 72.7, 61.9, 58.2, 50.8, 35.8, 34.0, 31.6 and 27.4. IR; ν_{max} (KBr), 3300, 2966, 1637, 1530, 1448, 1369, 1235, 1183, 1105, 1073, 1029, 966, 745, 698 cm⁻¹.

The starting material, 2R-(2,2-dimethyl-5-oxo-1-[1,3]dioxolan-4S-yl)-5-phenyl-hex-4-enoic acid 2,3,4,5,6-pentafluorophenyl ester, was prepared by methods analogous to those described in WO 94/02447, substituting cinnamyl bromide for methallyl iodide.

EXAMPLE 10

N⁴-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-(3-phenyl-propyl)-succinamide

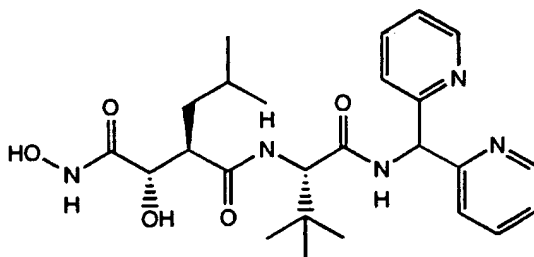


The title compound was prepared by analogy with Example 9. The cinnamyl sidechain was saturated by catalytic transfer hydrogenation (hydrogen gas, 10% palladium on charcoal in ethanol) at the penultimate step.

White solid (mixture of diastereomers). m.p. 86-88°C. ¹H-NMR; δ (CD₃OD), 7.23-7.01 (15H, m), 6.10 (1H, d, J = 3.7Hz), 4.36 (0.6H, s), 4.29 (0.4H, s), 4.18 (0.4H, d, J = 3.9Hz), 3.95 (0.6H, d, J=6.9Hz), 2.80-2.76 (1H, m), 2.51-2.39 (2H, m), 1.69-1.36 (4H, m) and 0.86 (9H, s). ¹³C-NMR; δ (CD₃OD), 175.5, 171.9, 171.5, 143.3, 142.7, 130.0, 129.5, 128.5, 128.2, 126.8, 73.2, 61.9, 58.1, 51.1, 50.1, 36.8, 35.7, 30.6, 30.1 and 27.3. IR; ν_{max} (KBr), 3300, 2955, 1641, 1529, 1496, 1452, 1369, 1234, 1077, 1029, 750 and 699 cm⁻¹.

EXAMPLE 11

N⁴-{1S-[(Di-pyridin-2-yl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-2S,N¹-dihydroxy-3R-isobutyl-succinamide

STEP A:

C,C-Di-pyridin-2-yl-methylamine

To a solution of di-2-pyridyl ketone (1.84 g, 10 mmol) and ammonium acetate (7.7 g, 100 mmol) in anhydrous methanol (30 ml) was added sodium cyanoborohydride (1.26 g, 20 mmol) and the resulting solution heated at reflux for 5 hours. The reaction mixture was then cooled in an ice bath and acidified to pH 2 with concentrated HCl. Solvent was removed under reduced pressure and the residue dissolved in water (30 ml), washed with ether (3 x 10 ml) then basified to pH 10 with solid sodium hydroxide. The solution was then extracted with dichloromethane (3 x 20 ml) and the combined organic phase dried over anhydrous MgSO₄, filtered and concentrated to a brown oil (1.6 g, 86%). The crude product was used directly in the next step.

STEP B:

N^α-2S-*tert*-Butoxycarbonylamino-N-(Di-pyridin-2-yl-methyl)-3,3-dimethyl-butylamide

A solution of N^α-2-*tert*-butoxycarbonylamino-L-*tert*-leucine (1.98 g, 8.6 mmol) in DMF (15 ml) was cooled to 0°C and treated with HOBT (1.39 g, 10.3 mmol) and EDC (1.98 g, 10.3 mmol). The reaction mixture was allowed to warm slowly to room temperature

and stirred for three hours. A solution of C,C-di-pyridin-2-yl-methylamine (1.6 g, 8.6 mmol) was added and the reaction mixture stirred at room temperature overnight. Solvent was evaporated and the residue dissolved in dichloromethane (30 ml). The solution was washed with water (2 x 20 ml) and brine (20 ml). The organic phase was separated, dried over anhydrous MgSO_4 , filtered and concentrated to a yellow oil. The crude product was purified by column chromatography (silica gel, 50% ethyl acetate in hexane) to give the title compound as a pale yellow solid (1.29 g, 38%). $^1\text{H-NMR}$; δ (CDCl_3): 8.55 (2H, m), 8.15 (1H, d, $J = 6.3$ Hz), 7.61 (2H, m), 7.45 (1H, d, $J = 7.5$ Hz), 7.38 (1H, d, $J = 7.6$ Hz), 7.15 (2H, m), 6.19 (1H, d, $J = 6.4$ Hz), 5.29 (1H, d, $J = 9.2$ Hz), 4.07 (1H, d, $J = 9.2$ Hz), 1.43 (9H, s) and 0.99 (9H, s).

STEP C:

N^o-2S-Amino-N-(di-pyridin-2-yl-methyl)-3,3-dimethyl-butylamide

N^o-2S-*tert*-Butoxycarbonylamino-N-(di-pyridin-2-yl-methyl)-3,3-dimethyl-butylamide (1.29 g, 3.24 mmol) was dissolved in methanol (5 ml) and added to a cooled, 2M solution of hydrochloric acid in ethyl acetate (25 ml). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated under reduced pressure and the residue dissolved in methanol (15 ml) and water (5 ml). Amberlite OH- resin was added until the solution reached pH 8. The resin was removed by filtration, washed well with methanol, and the combined filtrates concentrated at reduced pressure to provide the title compound as a yellow solid (1.10 g, 100%). $^1\text{H-NMR}$; δ (CDCl_3): 8.68 (1H, d, $J = 6.3$ Hz), 8.53 (2H, m), 7.63 (2H, m), 7.41 (2H, dd, $J = 16.7, 8.7$ Hz), 7.14 (2H, m), 6.24 (1H, d, $J = 6.6$ Hz), 3.45 (1H, d, $J = 11.1$ Hz), 3.20 (2H, br s) and 1.01 (9H, s).

The title compound was then prepared by methods analogous to those described in Example 1:

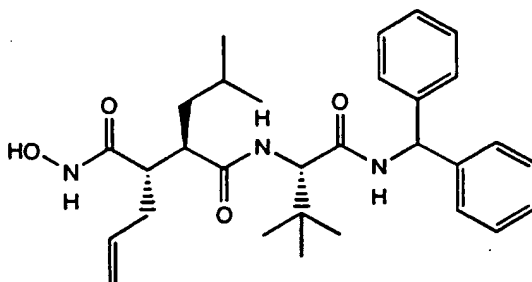
N⁴-{1S-[(Di-pyridin-2-yl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-2S,N¹-dihydroxy-3R-

isobutyl-succinamide

White solid. m.p. 98-106°C. $^1\text{H-NMR}$; δ (CD_3OD) 8.39 (2H, dd, $J = 2.2\text{Hz}$), 7.69 (2H, dd, $J = 7.7\text{Hz}$), 7.38 (2H, d, $J = 7.8\text{Hz}$), 7.20 (2H, dd, $J = 6.4, 5.0\text{Hz}$), 6.18 (1H, s), 4.32 (1H, s), 3.95 (1H, d, $J = 6.2\text{Hz}$), 2.79 (1H, m), 1.53 (1H, m), 1.41 (1H, m), 1.14 (1H, m), 0.90 (9H, s) and 0.73 (6H, dd, $J = 7.3\text{Hz}$). $^{13}\text{C-NMR}$; δ (CD_3OD): 175.8, 172.3, 171.5, 160.0, 159.8, 150.0, 149.7, 139.1, 138.9, 124.2, 124.0, 123.7, 73.1, 62.4, 60.7, 39.5, 35.4, 27.2, 26.9, 23.8 and 22.3. IR; ν_{max} (KBr) 3318, 2962, 1653, 1593, 1522, 1368, 1096, 1018 and 754 cm^{-1} .

EXAMPLE 12

2S-Allyl-N⁴-[1S-(benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-N¹-hydroxy-3R-isobutyl-succinamide

STEP A:

2R,S-{1R-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propylcarbamoyl]-3-methylbutyl}-pent-4-enoic acid *tert*-butyl ester

2R,S-Allyl-3R-isobutyl-succinic acid 4-*tert*-butyl ester (mixture of diastereoisomers, 3:1,

SR:RR; prepared according to WO 94/21625) (1.82 g, 6.76 mmol) was dissolved in DMF (80 ml) and cooled to 0°C, during the addition of HOBt (1.09 g, 8.11 mmol) and EDC (1.60 g, 8.11 mmol). The reaction mixture was stirred at room temperature for 5 hours and L-*tert*-leucine-N-benzhydrylamide (2.00 g, 6.76 mmol) was added. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (150 ml) and washed with 1N HCl (100 ml) and 1M Na₂CO₃ (100 ml). The organic phase was separated, dried over anhydrous MgSO₄, filtered and concentrated to a yellow oil. The crude product was purified by column chromatography (silica gel, 20% ethyl acetate in hexane) to give the title compound as a white foam (1.91 g, 52%; mixture of diastereoisomers, 5:1, SRS:RRS). ¹H-NMR; δ (CDCl₃, major diastereoisomer), 7.35 - 7.15 (11H, m), 6.37 - 6.21 (2H, m), 5.73 - 5.67 (1H, m), 5.06 - 4.99 (1H, m), 4.28 (1H, d, J = 9.2 Hz), 2.59 - 2.22 (4H, br m), 1.62 - 1.59 (1H, m), 1.44 (9H, s), 1.40 - 1.22 (1H, m), 1.20 - 1.00 (1H, m), 1.01 (9H, s), 0.83 (3H, d, J = 7.6 Hz) and 0.80 (3H, d, J = 6.5 Hz).

STEP B:

2S-{1R-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propylcarbamoyl]-3-methylbutyl}-pent-4-enoic acid

2R,S-{1R-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propylcarbamoyl]-3-methylbutyl}-pent-4-enoic acid *tert*-butyl ester (5:1, SRS:RRS from above) (1.91 g, 3.48 mmol) was dissolved in dichloromethane (6 ml) and TFA (6 ml) and the reaction mixture was stored at 4°C overnight. The solvent was removed under reduced pressure and the residue was azeotroped with toluene (5x50 ml). The crude product was recrystallised from ethyl acetate to give the title compound as a white crystalline solid (1.20 g, 71%; single diastereoisomer). ¹H-NMR; δ (CD₃OD), 8.84 (1H, d, J = 8.5 Hz), 7.92 (1H, d, J = 9.1 Hz), 7.25 - 7.08 (10H, m), 6.10 (1H, d, J = 8.5 Hz), 5.73 - 5.56 (1H, m), 4.96 - 4.86 (2H, m), 4.37 (1H, d, J = 9.4 Hz), 3.21 - 3.19 (1H, m), 2.56 - 2.45 (1H, m), 2.19 - 2.14 (2H, m), 1.62 - 1.48 (1H, m), 1.30 - 1.15 (1H, m), 1.10 - 1.07 (1H, m), 0.88 (9H, s), 0.81 (3H, d, J = 6.8 Hz) and 0.78 (3H, d, J = 7.0 Hz).

STEP C:

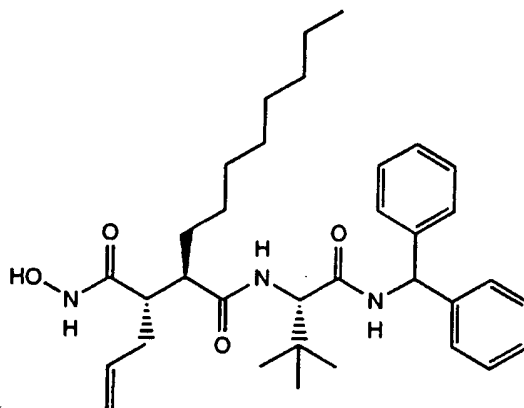
2S-Allyl-N⁴-[1S-(benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-N¹-hydroxy-3R-isobutyl-succinamide

To a solution of 2S-{1R-[1S-(benzhydryl-carbamoyl)-2,2-dimethyl-propylcarbamoyl]-3-methylbutyl}-pent-4-enoic acid (1.20 g, 2.44 mmol) in DMF (100 ml), HOBt (0.39 g, 2.93 mmol) and EDC (0.58 g, 2.93 mmol) were added. The reaction mixture was stirred for 6 hours at room temperature before hydroxylamine hydrochloride (0.25 g, 3.66 mmol) and NMM (0.40 ml, 3.66 mmol) were added. The reaction mixture was stirred for 2 days. The solvent was removed and the residue was suspended between ether (50 ml) and water (50 ml) for 3 hours. The product was filtered, suspended in ethyl acetate (100 ml) and refluxed for a few minutes. The product was filtered and dried to leave a white crystalline solid (1.082 g, 87%). m.p. 220.5 - 221°C. ¹H-NMR; δ (CD₃OD), 8.83 (1H, d, J = 8.4 Hz), 8.02 (1H, d, J = 9.5 Hz), 7.21 - 7.08 (10H, br m), 6.08 (1H, d, J = 8.6 Hz), 5.61 - 5.48 (1H, br m), 4.92 - 4.85 (2H, m), 4.37 (1H, d, J = 9.3 Hz), 2.62 - 2.55 (1H, m), 2.28 - 1.98 (3H, m), 1.47 - 1.36 (1H, m), 1.30 - 1.17 (1H, m), 1.02 - 0.91 (10H, m), 0.67 (3H, d, J = 6.3 Hz) and 0.65 (3H, d, J = 6.4 Hz). ¹³C-NMR; δ (CD₃OD), 176.5, 172.4, 171.7, 143.0, 142.9, 136.0, 129.6, 129.4, 129.1, 128.5, 128.2, 117.5, 62.3, 58.0, 48.1, 41.8, 36.4, 35.5, 27.4, 27.0, 24.7, 21.7 and 14.5. IR; ν_{\max} (KBr), 3295, 2954, 1637, 1525 and 699 cm⁻¹.

The following additional compound was prepared according to the methods of Example 12. The starting material 2R,S-Allyl-3R-octyl-succinic acid 4-*tert*-butyl ester was prepared by methods analogous to those described in WO 94/21625, substituting *n*-decanoyl chloride for 4-methyl-pentanoyl chloride.

EXAMPLE 13

2S-Allyl-N⁴-[1S-(benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-N¹-hydroxy-3R-octyl - succinamide



White solid. m.p. 219 - 219.5°C. $^1\text{H-NMR}$; δ (CD_3OD), 8.84 (1H, d, $J = 8.6$ Hz), 8.04 (1H, d, $J = 9.3$ Hz), 7.26 - 7.08 (10H, br m), 6.10 (1H, d, $J = 8.6$ Hz), 5.65 - 5.48 (1H, m), 4.93 - 4.85 (2H, m), 4.38 (1H, d, $J = 9.4$ Hz), 2.59 - 2.48 (1H, m), 2.24 - 2.13 (2H, m), 2.07 - 1.97 (1H, m), 1.37 - 0.99 (14H, br m), 0.89 (9H, s) and 0.78 (3H, t, $J = 6.5$ Hz). $^{13}\text{C-NMR}$; δ (CD_3OD), 176.6, 172.4, 171.7, 171.6, 143.0, 142.8, 136.0, 129.5, 129.4, 129.1, 128.5, 128.4, 128.1, 117.5, 62.0, 58.0, 57.9, 49.8, 47.6, 36.4, 35.4, 33.0, 32.6, 30.8, 30.4, 28.2, 27.3, 23.7 and 14.5. IR; ν_{max} (KBr), 3295, 2931, 1637, 1525, 1372 and 697 cm^{-1} . Found: C 70.47, H 8.67, N 7.54%; $\text{C}_{34}\text{H}_{49}\text{N}_3\text{O}_4 \cdot 0.9\text{H}_2\text{O}$ requires C 70.41, H 8.83, N 7.24%.

BIOLOGICAL EXAMPLE

The following table compares the *in vitro* potencies of compounds of the present invention against stromelysin-1, matrilysin, 72KDa gelatinase and human fibroblast collagenase. Data for two compounds known in the art where $\text{R}_4 = \text{CH}_3$ (Comparators 1 and 2) are included.

Comparator 1: 2S,N¹-Dihydroxy-N⁴-(2,2-dimethyl-1S-methylcarbamoyl-propyl)-3R-isobutyl-succinamide

Comparator 2: 2S-Allyl-N⁴-(2,2-dimethyl-1S-methylcarbamoyl-propyl)-N¹-hydroxy-3R-isobutyl-succinamide

The potency of compounds of the present invention as inhibitors of human fibroblast collagenase was determined by the procedure of Cawston and Barrett, (*Anal. Biochem.*, **99**, 340-345, 1979), hereby incorporated by reference, whereby a 1mM solution of the compound being tested, or a dilution thereof, was incubated at 37°C for 16 hours with collagen and collagenase (buffered with 25mM Hepes, pH 7.5 containing 5mM CaCl₂, 0.05% Brij 35 and 0.02% NaN₃). The collagen was acetylated ¹⁴C collagen prepared by the method of Cawston and Murphy, (*Methods in Enzymology*, **80**, 711, 1981), hereby incorporated by reference. The samples were centrifuged to sediment undigested collagen, and an aliquot of the radioactive supernatant removed for assay on a scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1mM of the test compound, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the result reported below as that of inhibitor concentration effecting 50% inhibition of the collagenase activity (IC₅₀).

The potency of compounds of the invention as inhibitors of stromelysin-1 was determined by the procedure of Cawston *et al.*, (*Biochem. J.*, **195**, 159-165, 1981), hereby incorporated by reference, whereby a 1mM solution of the compound being tested, or a dilution thereof, was incubated at 37°C for 16 hours with stromelysin and ¹⁴C acetate casein (buffered with 25mM Hepes, pH 7.5 containing 5mM CaCl₂, 0.05% Brij 35 and 0.02% NaN₃). The casein was acetylated ¹⁴C casein prepared by the method of Cawston *et al.* (*ibid.*). The stromelysin activity in the presence of 1mM of the test compound, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the result reported below as that of inhibitor concentration effecting 50% inhibition of the stromelysin activity (IC₅₀).

The potency of compounds of the invention as inhibitors of 72 kDa gelatinase was determined by a procedure based on the method of Sellers *et al.*, *Biochem. J.*, **171**, 493-496 (1979). 72 kDa gelatinase, derived from RPMI-7951 cells was purified by

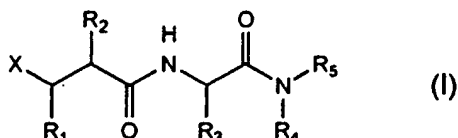
gelatin-agarose chromatography. The enzyme was activated by incubation with aminophenyl mercuric acetate and approximately 0.05 units was incubated with 50µg [¹⁴C]-radiolabelled gelatin in an appropriate buffer for 16 hours at 37°C. At the end of the incubation 50µg bovine serum albumin, together with trichloroacetic acid (final concentration 16%) were added to stop the reaction and to precipitate any undegraded substrate. The reaction tubes were placed on ice for 15 minutes before centrifugation at 10,000g for 15 minutes to sediment the precipitated substrate. A 200 µl aliquot of the reaction supernatant was removed and the radioactivity determined by liquid scintillation counting. The effect of the inhibitors was determined by reference to a dose response curve. The IC₅₀ (the concentration of inhibitor required to cause a 50% decrease in enzyme activity) was obtained by fitting a curve to the data and computing the concentration of inhibitor required to achieve 50% inhibition of the enzyme. For each IC₅₀ determination, the effect on gelatinase activity of at least 8 concentrations of the inhibitor were examined. The inhibitors were dissolved DMSO and diluted to the appropriate test concentrations.

The potency of the compounds of the invention as inhibitors of recombinant matrilysin (PUMP-1) was determined using an assay which was adapted from the assay used to measure the stromelysin activity. A solution of the compound being tested, dissolved in dimethyl sulphoxide (DMSO) was incubated at 37°C for 16 hours with matrilysin and ¹⁴C- acetylated casein (buffered with 50mM Tris HCl, pH 7.6 containing 5mM CaCl₂, 0.05% (v/v) Brij 35). The reaction was terminated by the addition of trichloroacetic acid (TCA), and the substrate separated from soluble degradation products by centrifugation. The radioactivity associated with the TCA-soluble products released from casein by matrilysin was determined by liquid scintillation counting. The effect of BB-2516 was determined by examining a dose-response curve. The concentration of inhibitor required to cause a 50% decrease in enzyme activity (IC₅₀) was obtained by manual interpolation from the graph.

Test Compound	<i>In vitro</i> inhibitory activity IC ₅₀ (nM)			
	Fib. Collag. (MMP-1)	Gelatinase A (MMP-2)	Stromelysin-1 (MMP-3)	Matrilysin (MMP-7)
Comparator 1	5	6	200	20
Example 1	600	3000	50	4
Example 2	2000	17000	200	70
Example 3	400	2000	200	10
Example 4	400	500	60	9
Example 5	700	600	100	9
Example 6	2000	600	200	15
Example 7	40%I @ 100μM	50%I @ 100μM	20000	NT
Example 8	700	1000	20	9
Example 9	30%I @ 100μM	40000	800	500
Example 10	10000	8000	90	1000
Example 11	300	1000	200	20
Comparator 2	4	15	80	20
Example 12	800	40000	80	30
Example 13	30000	20000	60	400

Claims:

1. A compound of formula I



wherein

X is a $-\text{CO}_2\text{H}$ or $-\text{CONHOH}$ group;

R_1 is $(\text{C}_1\text{-C}_6)\text{alkyl}$; $(\text{C}_2\text{-C}_6)\text{alkenyl}$; phenyl; substituted phenyl; phenyl $(\text{C}_1\text{-C}_6)\text{alkyl}$; substituted phenyl $(\text{C}_1\text{-C}_6)\text{alkyl}$; heterocyclyl; substituted heterocyclyl; heterocyclyl $(\text{C}_1\text{-C}_6)\text{alkyl}$; substituted heterocyclyl $(\text{C}_1\text{-C}_6)\text{alkyl}$; a group $\text{BSO}_n\text{A-}$ wherein n is 0, 1 or 2 and B is hydrogen or a $(\text{C}_1\text{-C}_6)\text{ alkyl}$, phenyl, substituted phenyl, heterocyclyl, $(\text{C}_1\text{-C}_6)\text{acyl}$, phenacyl or substituted phenacyl group, and A represents $(\text{C}_1\text{-C}_6)\text{alkyl}$; amino; protected amino; acylamino; OH ; SH ; $(\text{C}_1\text{-C}_6)\text{alkoxy}$; $(\text{C}_1\text{-C}_6)\text{alkylamino}$; di- $(\text{C}_1\text{-C}_6)\text{alkylamino}$; $(\text{C}_1\text{-C}_6)\text{alkylthio}$; aryl $(\text{C}_1\text{-C}_6)\text{alkyl}$; amino $(\text{C}_1\text{-C}_6)\text{alkyl}$; hydroxy $(\text{C}_1\text{-C}_6)\text{alkyl}$; mercapto $(\text{C}_1\text{-C}_6)\text{alkyl}$ or carboxy $(\text{C}_1\text{-C}_6)\text{alkyl}$ wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated; lower alkyl substituted by carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, or carboxy-lower alkanoylamino;

R_2 is a $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_2\text{-C}_6)\text{alkenyl}$, $(\text{C}_2\text{-C}_6)\text{alkynyl}$, phenyl $(\text{C}_1\text{-C}_6)\text{alkyl}$, heteroaryl $(\text{C}_1\text{-C}_6)\text{alkyl}$, cycloalkyl $(\text{C}_1\text{-C}_6)\text{alkyl}$ or cycloalkenyl $(\text{C}_1\text{-C}_6)\text{ alkyl}$ group, any one of which may be optionally substituted by one or more substituents selected from $(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{S}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{OCH}_2\text{Ph}$ wherein the phenyl group may be optionally substituted, halo and cyano $(-\text{CN})$;

R_3 is the characterising group of a natural or non-natural α amino acid in which any functional groups may be protected;

R_4 is a group $-\text{CHR}^x\text{R}^y$ wherein R^x and R^y independently represent optionally substituted phenyl or monocyclic heteroaryl rings, which optionally may be linked covalently to each other by a bond or by a C_1 - C_4 alkylene or C_2 - C_4 alkenylene bridge, either of which may be interrupted by an O or S atom;

R_5 is hydrogen or a $(\text{C}_1\text{-C}_6)$ alkyl group;

or a salt, hydrate or solvate thereof.

2. A compound as claimed in claim 1 wherein the stereochemistry is as follows:

C atom carrying the R_1 and X groups - S,

C atom carrying the R_2 group - R,

C atom carrying the R_3 group - S,

C atom carrying the R^x and R^y groups - R or S

3. A compound as claimed in claim 1 or claim 2 wherein R_1 is methyl, ethyl, hydroxyl, methoxy, allyl, thienylsulphanylmethyl, thienylsulphinylmethyl, thienylsulphonylmethyl or phthalimidomethyl.

4. A compound as claimed in any one of the preceding claims wherein R_2 is isobutyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, cyclohexylpropyl, phenylpropyl, phenylpropenyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, pyridine-4-ylpropyl, phenylbutyl, benzyloxybutyl, propyloxymethyl or propylsulphanyl.

5. A compound as claimed in any one of the preceding claims wherein R_3 is:

$(\text{C}_1\text{-C}_6)$ alkyl, benzyl, hydroxybenzyl, benzyloxybenzyl, $(\text{C}_1\text{-C}_6)$ alkoxybenzyl, or

benzyloxy(C₁-C₆)alkyl group; or

the characterising group of a natural α amino acid, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group -[Alk]_nR₆ where Alk is a (C₁-C₆)alkyl or (C₂-C₆)alkenyl group optionally interrupted by one or more -O-, or -S- atoms or -N(R₇)- groups [where R₇ is a hydrogen atom or a (C₁-C₆)alkyl group], n is 0 or 1, and R₆ is an optionally substituted cycloalkyl or cycloalkenyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -OCH₂COR₈ where R₈ is hydroxyl, amino, (C₁-C₆)alkoxy, phenyl(C₁-C₆)alkoxy, (C₁-C₆)alkylamino, di((C₁-C₆)alkyl)amino, phenyl(C₁-C₆)alkylamino, the residue of an amino acid or acid halide, ester or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine, α or β alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid; or

a heterocyclic((C₁-C₆)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C₁-C₆)alkoxy, cyano, (C₁-C₆)alkanoyl, trifluoromethyl (C₁-C₆)alkyl, hydroxy, formyl, amino, (C₁-C₆)alkylamino, di-(C₁-C₆)alkylamino, mercapto, (C₁-C₆)alkylthio, hydroxy(C₁-C₆)alkyl, mercapto(C₁-C₆)alkyl or (C₁-C₆)alkylphenylmethyl;

6. A compound as claimed in any one of claims 1 to 4 wherein R₃ is a group CR_aR_bR_c in which:

each of R_a, R_b and R_c is independently hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, phenyl(C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, the foregoing being

subject to the proviso that R_a , R_b and R_c are not all hydrogen; or

R_c is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl (C_1-C_6) alkyl, or (C_3-C_8) cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a , R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl (C_1-C_6) alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 3- to 8-membered heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, -CO₂H, (C_1-C_4) perfluoroalkyl, -CH₂OH, -CO₂ (C_1-C_6) alkyl, -O (C_1-C_6) alkyl, -O (C_2-C_6) alkenyl, -S (C_1-C_6) alkyl, -SO (C_1-C_6) alkyl, -SO₂ (C_1-C_6) alkyl, -S (C_2-C_6) alkenyl, -SO (C_2-C_6) alkenyl, -SO₂ (C_2-C_6) alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO₂- and W represents a phenyl, phenylalkyl, (C_3-C_8) cycloalkyl, (C_3-C_8) cycloalkylalkyl, (C_4-C_8) cycloalkenyl, (C_4-C_8) cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO₂H, -CO₂ (C_1-C_6) alkyl, -CONH₂, -CONH (C_1-C_6) alkyl, -CONH (C_1-C_6) alkyl)₂, -CHO, -CH₂OH, (C_1-C_4) perfluoroalkyl, -O (C_1-C_6) alkyl, -S (C_1-C_6) alkyl, -SO (C_1-C_6) alkyl, -SO₂ (C_1-C_6) alkyl, -NO₂, -NH₂, -NH (C_1-C_6) alkyl, -N $((C_1-C_6)$ alkyl)₂, -NHCO (C_1-C_6) alkyl, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_8) cycloalkyl, (C_4-C_8) cycloalkenyl, phenyl or benzyl.:

7. A compound as claimed in any one of claims 1 to 4 wherein

R_3 is benzyl, iso-butyl, t-butyl, 1-benzylthio-1-methylethyl, 1-hydroxy-1-methylethyl or 1-mercapto-1-methylethyl.

8. A compound as claimed in any one of the preceding claims wherein R_4 is a group $-CHR^xR^y$, in which of R^x and R^y groups are independently selected from optionally substituted phenyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, trizolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

9. A compound as claimed in claim 8 wherein R^x and R^y are independently phenyl, 2-fluorophenyl, 4-fluorophenyl, 2-pyridyl or 4-chlorophenyl.

10. A compound as claimed in any one of claims 1 to 7 in which R_4 is optionally substituted 9-H-fluoren-9-yl.

11. A compound as claimed in any one of the preceding claims in which R_5 is hydrogen.

12. A compound selected from the group consisting of;

N^4 -(1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl)-2S, N^1 -dihydroxy-3R-isobutyl-succinamide;

N^4 -(1S-(9H-Fluoren-9-ylcarbamoyl)-2,2-dimethyl-propyl)-2S, N^1 -dihydroxy-3R-isobutyl-succinamide;

N^4 -(1S-(((4-Chloro-phenyl)-phenyl-methyl)-carbamoyl)-2,2-dimethyl-propyl)-2R, N^1 -dihydroxy-3R-isobutyl-succinamide;

N^4 -(1S-(((4-Fluoro-phenyl)-phenyl-methyl)-carbamoyl)-2,2-dimethyl-propyl)-2S, N^1 -dihydroxy-3-isobutyl-succinamide;

N^4 -(1S-(((2-Fluoro-phenyl)-phenyl-methyl)-carbamoyl)-2,2-dimethyl-propyl)-2S, N^1 -dihydroxy-3R-isobutyl-succinamide;

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propylcarbamoyl]-2S-methoxy-5R-methyl-hexanoic acid;

N⁴-[1S-(Benzhydryl-carbamoyl)-2-hydroxy-2-methyl-propyl]-2S,N¹-dihydroxy-2-isobutyl-3R-methoxy-succinamide;

N⁴-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-(3-phenyl-allyl)-succinamide;

N⁴-[1S-(Benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-2S,N¹-dihydroxy-3R-(3-phenyl-propyl)-succinamide;

N⁴-{1S-[(Di-pyridin-2-yl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-2S,N¹-dihydroxy-3R-isobutyl-succinamide;

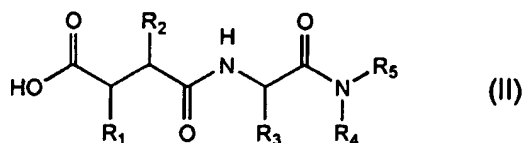
2S-Allyl-N⁴-[1S-(benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-N¹-hydroxy-3R-isobutyl-succinamide; and

2S-Allyl-N⁴-[1S-(benzhydryl-carbamoyl)-2,2-dimethyl-propyl]-N¹-hydroxy-3R-octyl-succinamide;

and salts, solvates or hydrates thereof.

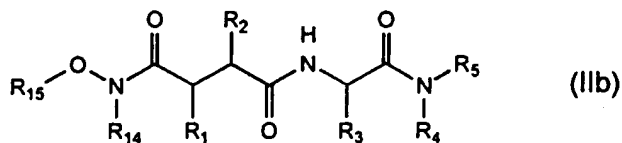
13. A process for the preparation of a compound as claimed in claim 1 in which X is a hydroxamic acid group (-CONHOH), which process comprises:

(a) causing an acid of general formula (II)



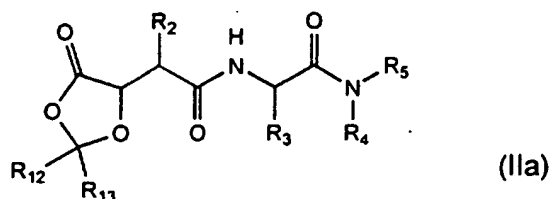
or an activated derivative thereof to react with hydroxylamine, O-protected hydroxylamine, or an N,O-diprotected hydroxylamine, or a salt thereof, R_1 , R_2 , R_3 , R_4 , and R_5 being as defined in general formula (I) except that any substituents in R_1 , R_2 , R_3 , R_4 , and R_5 which are potentially reactive with hydroxylamine, O-protected hydroxylamine, the N,O-diprotected hydroxylamine or their salts may themselves be protected from such reaction, then removing any protecting groups from the resultant hydroxamic acid moiety and from any protected substituents in R_1 , R_2 , R_3 , R_4 , and R_5 ; or

(b) deprotecting a diprotected hydroxamic acid derivative of formula (IIb)



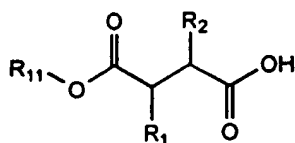
in which R_1 , R_2 , R_3 , R_4 , and R_5 are as defined in general formula (I), R_{14} is an amino protecting group and R_{15} is a hydroxyl protecting group.

14. A process as claimed in claim 13 wherein in step (a) (in the special case where R_1 in compound (I) is hydroxy) the hydroxy group R_1 and the adjacent carboxyl group are simultaneously protected as a dioxalone of formula (IIa):

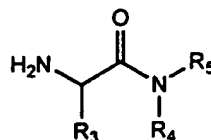


wherein the groups R_{12} and R_{13} are derived from a dioxalone forming reagent, and the dioxalone ring being is opened by the reaction with hydroxylamine to give the required hydroxamic acid derivative of formula (I).

15. A process for the preparation of a compound as claimed in claim 1 in which X is a carboxylic acid group (-COOH) which process comprises coupling an acid of formula (III) or an activated derivative thereof with an amine of formula (IV)



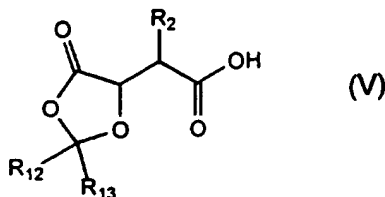
(III)



(IV)

wherein R_1 , R_2 , R_3 , R_4 , and R_5 are as defined in general formula (I) except that any substituents in R_1 , R_2 , R_3 , R_4 , and R_5 which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and R_{11} represents a hydroxy protecting group, and subsequently removing the protecting group R_{11} , and any protecting groups from R_1 , R_2 , R_3 , R_4 , and R_5 .

16. A process as claimed in claim 15 wherein (in the special case where R_1 in compound (I) is hydroxy) compound (III) has the formula (V):



(V)

wherein R_2 is as defined in general formula (I) and the groups R_{12} and R_{13} are

derived from a dioxalone forming reagent.

17. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1 to 12 together with a pharmaceutically or veterinarily acceptable excipient or carrier.

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.
PCT/GB 96/00965

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C259/06 C07C237/22 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	GB,A,2 268 933 (BRITISH BIO TECHNOLOGY) 26 January 1994 cited in the application see claims; examples & WO,A,94 02446	1,17
A	--- WO,A,94 21625 (BRITISH BIO TECHNOLOGY ;CRIMMIN MICHAEL JOHN (GB); BECKETT PAUL RA) 29 September 1994 cited in the application see claims; examples	1,17
A	--- EP,A,0 575 844 (HOFFMANN LA ROCHE) 29 December 1993 cited in the application see claims; examples -----	1,17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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A document member of the same patent family

Date of the actual completion of the international search

23 July 1996

Date of mailing of the international search report

- 2. 08. 96

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Seufert, G

INTERNATIONAL SEARCH REPORT

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PCT/GB 96/00965

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